EDITORIAL

Growth hormone deficiency and cardiovascular risk: do we need additional markers?

M. Gola · A. Giustina

Atherosclerosis, a chronic inflammatory disease of large and medium size arteries, continues to be the leading cause of cardiovascular events and one of the most common causes of mortality and cardiovascular disease [1]. Atherosclerotic lesion progression depends on chronic inflammation in the artery wall, and the innate and adaptive immune responses are involved in these processes [2]. In recent years, several new circulating markers, including C-reactive protein (CRP), fibrinogen, lipoprotein(a) (Lp(a)), and homocysteine [3–5] have been proposed as potential risk factors for atherothrombotic vascular disease.

It is known that alteration of the GH/IGF-1 axis contributes to determining cardiovascular disease as suggested by clinical studies reporting increased risk for cardiovascular morbidity and mortality in adults with GH deficiency (GHD) [6, 7]. Epidemiological studies in the general population have also shown that IGF-1 levels in the low-normal range are associated with an increased risk of ischemic heart disease and stroke outcome [8, 9]. Moreover, activity of GH/IGF-1 axis decreases with aging [10] and hypothyroidism [11] both conditions of increased cardiovascular risk.

M. Gola (✉) · A. Giustina
Department of Medical and Surgical Sciences, University of Brescia, Brescia, Italy
e-mail: monica.gola10@tiscali.it

A. Giustina
e-mail: a.giustina@libero.it

M. Gola
Department of Internal Medicine, Mirandola Hospital, Modena, Italy

A. Giustina
Endocrine Service, Montichiari Hospital, Via Ciotti 154, 25018 Montichiari, Brescia, Italy

Hypopituitary GHD adults have been shown to have an increased number of atheromatous plaques in carotid and femoral arteries, as compared with control individuals. Other signs of atheromatosis found in GHD patients include an increased intima-media thickness, more pronounced stiffness of carotid arteries, and less aortic distensibility [12].

GHD is also associated with abnormalities in body composition that may have an impact on cardiovascular risk. In fact, a clustering of cardiovascular clinical risk factors has been reported in GHD patients, including truncal adiposity and increased visceral fat, changes in body composition and insulin resistance, negative changes in lipid profiles and abnormal hemostatic factors [13].

Echocardiographic studies have demonstrated that adult patients with GHD have reduced left ventricular (LV) mass and impaired cardiac performance as shown by decreased ejection fraction and abnormal LV diastolic filling [14]. Other studies have reported decreased LV posterior wall thickness, without any difference in internal diameter or ejection fraction in patients with GHD versus those without GHD [15]. Despite many studies, although limited in follow-up time and in the number of patients, showing an improvement in GH-mediated both systolic and diastolic function by echocardiography or radionuclide angiography [14, 15], it remains unclear if there may be a direct favorable effects on cardiac function by physiological GH replacement therapy [16]. In fact, recently, Andreassen et al. [17] evaluated cardiac function before and during GH treatment using cardiac magnetic resonance imaging and measurement of circulating levels of B-type natriuretic-peptides. They showed that patients with untreated GHD had unchanged ejection and LV mass as compared with control subject. One year of adequate GH replacement therapy was not associated with significant increases in LV volume, ejection fraction, or LV mass. No changes in brain

natriuretic peptide levels compared to control subjects at baseline or during treatment were observed.

An unfavorable lipid profile is central in the pathogenesis of atherosclerosis, and the changes in lipids typical of GHD may help to explain the increased the cardiovascular risk in untreated GHD. Low IGF-I in GHD may be the primary mechanism underlying the abnormal body composition and central fat distribution and may also contribute to the hypercholesterolemia. Total and LDL cholesterol levels decrease significantly during short-term GH replacement therapy, but these initial effects have been reported to be lost during long-term therapy in some, even if not in all studies [18].

A chronic low-grade inflammation has been considered to play an important role in the atherosclerotic process of arterial wall. Serum markers of inflammation and in particular CRP may predict the risk for acute cardiovascular events in the general population [19]. Moreover, a bulk of evidence suggests that inflammatory status as expressed by CRP is a strong and independent predictor of severity of coronary artery disease [20].

Hypopituitary adults with GHD have also been shown to have higher baseline CRP and IL-6 levels when compared to healthy matched controls in some but not in all studies. Sesmilo et al. [21] reported in a randomized single-blind placebo-controlled trial that long-term growth hormone replacement in men reduced CRP levels, which were elevated at baseline, as well as decreased central fat. In combination with these data, the same authors reported the highest levels of CRP in hypopituitary adult women [22]. In this issue of endocrine, Li et al. [23] reported that pregnancy associated plasma protein A (PAPP-A) levels are significantly increased in GHD adults versus age and body weight matched controls. PAPP-A is a member of the matrix metalloproteinase family originally isolated in serum of pregnant women but also present in the serum of general population. PAPP-A has been recently included among markers of cardiovascular risk being associated both to the presence of carotid atherosclerosis and acute coronary syndrome [24, 25]. Li et al. [23] have not found any correlations between PAPP-A and CRP levels although also the latter were found to be increased in GHD patients. First, merit of Li paper is to confirm that a quite new marker of cardiovascular risk such as PAPP-A is increased in GHD patients [26]. However, one can argue that this does not add much to what we already know in this area. In our opinion this may not be true. In fact, interestingly PAPP-A is directly involved in the regulation of IGF-1 action by increasing its free and biologically active levels [23]. Therefore, the increase in PAPP-A may have a compensatory significance directly linked to GHD. This is a clear distinction with respect to the elevation of CRP which is at best an indirect expression of GHD. Furthermore, PAPP-A levels have been shown to be well correlated with parameters of glucose metabolism, as well as

with altered lipid profile (increase total cholesterol, triglycerides, and decreased HDL cholesterol) [23]. This may interestingly allow us to suggest PAPP-A as a bridge between GHD and insulin resistance, altered lipid profile, and cardiovascular risk.

Clearly, the clinical significance of any cardiovascular risk markers in GHD needs to be validated evaluating their behavior during GH substitutive treatment. In a recent study, Deepak et al. [27] reported a marked fall in CPR levels during physiological GH replacement in the absence of changes in body composition. Only a few data are available about the effect of GH treatment on PAPP-A in GHD. In fact, it has been shown that PAPP-A significantly decreased in a small group of GHD patients after 1 year of GH administration [26]. Interestingly, there are no definitive data in general on the benefit of GHD treatment on actual cardiovascular risk [28, 29]. In this respect, for the clinicians the correlation between the decrease of a biochemical marker with the reduction in cardiovascular events would be the only evidence for introducing this parameter in clinical practice. We are very far from this end point since interventional studies in GHD did not include recently discovered markers and when and if clinical evidence of cardiovascular benefits of GH replacement will be shown there will probably not be still any data on the role of "non traditional" markers. Nevertheless, although data from Li et al. [23] on PAPP-A cannot be translated immediately into clinical practice they have interesting pathophysiological implications in that this biochemical parameter could be hypothesized to be the first "pathophysiological" and not "generic" marker of cardiovascular risk in GHD patients.

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